

Silence of the Limbs

Pharmacological Symptomatic Treatment of Intermittent Claudication

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Abstract

Several oral “vasoactive” drugs claim to increase walking capacity in patients with intermittent claudication (IC). Naftidrofuryl, cilostazol, buflomedil, and pentoxifylline are the most studied molecules. Although spanning several decades, several studies underlying these claims were not properly designed, underpowered or showed clinically doubtful outcomes. The evidence for these “vasoactive” drugs has always been received with scepticism, creating the need for systematic reviews and meta-analyses. This brief review discusses the benefit-risk assessment of vasoactive drugs, by applying a systematic review to evaluate randomized, placebo-controlled trials.

Oral naftidrofuryl and cilostazol have an acceptable safety profile as well as sustained evidence (documented by Cochrane analyses) of increased walking capacity. Subsequently, these drugs entered recommendations for peripheral arterial disease (PAD). In contrast, buflomedil and pentoxifylline have limited and/or doubtful evidence to increase walking capacity. Moreover, there were safety concerns about the narrow therapeutic range of buflomedil. Most other “vasoactive” drugs were either inappropriately or insufficiently tested or showed no significant if not negative effects on IC. “Vasoactive” drugs are no substitutes for lifestyle or exercise therapy but are adjuvant treatment to the well-appreciated triad of cardiovascular prevention (antiplatelet agents, statins and ACE-inhibitors), of which statins in their own right have documented claims to significantly increase walking capacity.

“Vasoactive” drugs may have a place in the pharmacological management of symptomatic PAD in addition to the basic cardiovascular pharmacotherapy, when revascularization is not indicated, when exercise therapy is not feasible or when there is still insufficient benefit.

Key words: Intermittent claudication, randomized controlled clinical trial, systematic review, risk-benefit assessment, cardiovascular prevention, vasoactive agents, statins, cilostazol, naftidrofuryl, pentoxifylline, buflomedil

Introduction

Treating the symptoms of intermittent claudication (IC) with drugs has always been viewed with caution, because of lack of documented evidence of efficacy on symptoms and hard endpoints.

The pharmacological class of peripheral vasoactive agents is heterogeneous with multiple physiological actions. These drugs have been heavily promoted for decades, but many have been questioned and few are included in current guidelines. No single drug has gained full and widespread acceptance for use in IC.

Epidemiological surveys reveal that patients with peripheral arterial disease (PAD) and its co-morbidity are blatantly undertreated. Their risk modification is often not optimal and the cardiovascular co-morbidity underestimated ¹.

Finally, symptomatic PAD patients are often severely impaired as to functional status (walking distance) and quality of life.

Standard treatment

Lifestyle changes, management of risk factors and use of cardioprotective drugs are undoubtedly the first priority in the treatment of IC to inhibit progression of atherosclerotic disease and development of atherothrombotic complications in the cardiovascular tree. Basic treatment consists of an active policy of smoking cessation, supervised and unsupervised exercise training, control of diabetes, dyslipidemia, hypertension, correction of hypercoagulable states and antiplatelet therapy²⁻⁶. Moreover, some of these therapies, such as smoking cessation⁷, exercise programs⁸ and statins⁹ also have a symptomatic effect on walking distance (WD).

Revascularization

Second, there is also the choice of endovascular or surgical revascularization.

These procedures are readily available in most hospital settings and it is tempting to dilate or operate on stenotic vessels. Revascularization should only be considered when certain criteria are fulfilled and a global favourable benefit-risk ratio might be expected ¹⁰. Given the variable natural course of the disease, evaluation of the effect of invasive vascular therapy is complex. Long-term evaluation is needed. The clinical and scientific community is awaiting the results of the CLEVER (The Claudication Exercise Vs Endoluminal Revascularization) study ¹¹.

Other cardiovascular morbidity (coronary artery disease (CAD), atherosclerotic renal artery disease), which is closely associated with IC should be corrected, provided there is a prognostic potential ¹².

Symptomatic treatment

Is there still a place for the pharmacological treatment of the symptoms of IC, next to secondary prevention and a myriad of interventional options? Some patients remain symptomatic even after maximal application of secondary prevention measures or revascularization. Some patients have contra-indications for invasive treatment or have a personal preference for pharmacological therapy.

The aim is to separate the wheat from the chaff in the large class of presently available vasoactive drugs by determining for which substances sufficient evidence of symptomatic effect is available to support their use in IC patients.

How to assess risk and benefit of vasoactive drugs?

Safety assessment

In most, especially older, randomized controlled trials (RCTs) of vasoactive drugs, the section on safety is often limited to a statement such as “the drug was well tolerated”. Adverse event reporting was often only based on volunteered reporting and the trials were too small to detect low prevalence problems. A zero numerator does not mean all is safe¹³. Especially when dealing with old products, several sources of safety data should be consulted. Information from national and international safety databases should be critically analyzed and assessed for reporting bias. Case reports of serious adverse reactions should be traced with classical bibliographic searches, meticulous checking of conferences and proceedings, references of publications (snow balling), contact with the original study investigators, other researchers and the manufacturer.

Benefit assessment

Since there is no gold standard for the symptomatic treatment of IC, evidence on efficacy can only be obtained from placebo-controlled RCTs. It is clear that patients should receive optimal standard treatment.

Successful symptomatic treatment of IC means a relevant improvement in WD measured by a standardized exercise test. The relevance of changes of surrogate endpoints (temperature, viscosity) is not known as there is no correlation with clinical parameters.

Reviews or meta-analyses of trials on IC should be critically appraised, as in this scientific field the number of narrative reviews exceeds the number of original studies. Special attention for trial selection, publication bias and heterogeneity is needed¹⁴.

a) The trial selection process can only be appraised, when the search strategy, selection criteria, and data extraction choices are explicitly mentioned. At least 2 raters should assess the quality of the set of retrieved trials. Each study is checked for bias in internal and external validity¹⁵. When results are not reported in sufficient detail, an attempt has to be made to contact the author(s).

b) Publication bias in evidence based medicine is a serious limitation: presentation of the results can be biased or trials with negative results may not be reported.

Publication bias can theoretically be assessed through funnel plots¹⁶. However, the sample size of many studies of pharmacological treatment of IC is small. Hence funnel plots based on detection of a positive monotonic relationship between relative efficacy and sample size are of limited relevance here. All efforts should be taken to search for and to locate unpublished studies.

Trials should be meticulously traced. Besides bibliographic searches for trials and reviews, thorough searching of trial registers, hand searching, searching of proceedings and conferences, meticulous checking of references of publications (snow balling), contact with other researchers, and with the manufacturing company are all necessary.

c) Heterogeneity should always be discussed in a meta-analysis¹⁷. Clinical heterogeneity can be assessed qualitatively looking at similarities or differences between trials and can be reduced by predefined selection criteria.

Statistical heterogeneity can be assessed graphically by forest plots with χ^2 test. When there is an indication for significant heterogeneity the results should either not be summarised, or analysed with random effects models¹⁸.

Clinical relevance is a tricky issue in IC. How to define a responder? Does it mean $\geq 50\%$ improvement of baseline? Is a threshold of weighted mean difference (WMD) of at least 25 or 50 m relevant? These questions have not yet been answered definitely,

as the relationship between improvement in walking distance and maintenance of daily life activities and quality of life¹⁹ stills needs elucidation.

Results of our quest for evidence on risk and benefit of vasoactive drugs in IC

Based on evidence from RCTs, 3 groups emerged with regard to efficacy (table): I. drugs with an evidence base supporting claims of efficacy, II. drugs with limited and/or doubtful evidence of efficacy, III. drugs with no proven evidence of efficacy.

I. Drugs with an acceptable safety profile have an evidence base supporting claims of limited efficacy:

Naftidrofuryl (mostly used in Europe) has evidence from a meta-analysis based on individual patient data of 7 trials²⁰. Oral naftidrofuryl gives a significant improvement of painfree walking distance (PFWD) and maximum walking distance (MWD) over placebo (n=1266, WMD 48.44 m, 95%CI 35.94-60.95 and 88.9 m, 95%CI 29.94-147.87). There is evidence for improvement of quality of life²¹. Besides gastric problems, tolerance and safety are acceptable. A drawback of naftidrofuryl is the patient's compliance with a daily dosage of 3x200 mg. Reformulation of the drug with prolonged action might be considered.

Cilostazol (mostly used in the US) has evidence from a meta-analysis. Cilostazol 2x100 mg/day gives a significant improvement of PFWD and MWD²² (n= 1500, WMD 31.1 m, 95%CI 21.3-40.9 and 49.7 m, 95%CI 24.2-75.2, respectively). Cilostazol has potent antiplatelet activity and some clinical trials point into the direction of beneficial effect of cilostazol similar to other antiplatelet regimens^{23, 24} and on top of other antiplatelets as aspirin and clopidogrel²⁵.

As a phosphodiesterase-inhibitor, the drug is contra-indicated in heart failure and side effects include headache, diarrhoea, and dizziness but the overall safety profile is acceptable. Nowadays naftidrofuryl and cilostazol are the best candidates for symptomatic treatment of IC. Both are mentioned in the SIGN²⁶ and TASC II¹⁰ guidelines.

Statins have evidence from several RCTs for a beneficial effect on IC (PFWD: WMD 89.76 m, 95% CI 30.05-149.47, MWD: WMD 152 m, 95% CI 32.11-271.88)^{9, 27-30} besides their well known lipid lowering effects and benefit on cardiovascular and cerebrovascular morbidity and mortality. They also might play a beneficial role in pre-operative use in vascular surgery, in renal protection which further promotes them for standard use in the vulnerable PAD patients³¹⁻³⁵. Side effects include myalgia with risk of rhabdomyolysis, mainly in combination with other drugs, increased liver enzymes, central effects and polyneuritis³⁶.

II. Drugs with limited and/or doubtful evidence:

We briefly discuss buflomedil, registered in Europe, and pentoxifylline, registered in both Europe and the USA, for treatment of IC.

For *buflomedil*, in a systematic review 6 trials were selected but 4 of them excluded because of high risk of bias³⁷. The 2 remaining trials randomised a total of 127 participants to receive buflomedil or placebo for at least 3 months^{38, 39}. Both showed moderately positive results for improvement in PFWD (n=93, 75.1 m, 20.6-129.6; n=34, 80.6 m, 3.0-158.2, respectively) and MWD (n=93, 80.7 m, 9.4-152; n=34, 171.4 m, 51.3-291.5) with wide variation in benefit between participants. At least another 4 unpublished studies with negative results⁴⁰⁻⁴³, cited in a meta-analysis⁴⁴, exist. We could not retrieve the original reports for data extraction. This is a rare example of

documented publication bias and not just publication bias inferred from graphics or statistics.

In 1999 the French government commissioned a long-term trial of buflomedil, coinciding with concerns about potential toxicity of the product. The Limbs International Medical Buflomedil Trial was a large RCT in which limited improvement of a composite outcome was observed⁴⁵. In the editorial⁴⁶ the results were interpreted much more conservatively. No safety problems were mentioned in the trial. However, in 2006 safety concerns were raised in several countries because of lethal and non-lethal neurological and cardiovascular adverse events in cases of accidental and voluntary overdoses and in renal insufficiency⁴⁷. As a consequence, the 300 and 600 mg forms have been withdrawn from the market, the 150 mg dosage is kept with the only indication of IC⁴⁸

Given the limited evidence on efficacy and the narrow therapeutic range, the present benefit-risk ratio of buflomedil is considered as marginal.

With *pentoxifylline* several RCTs have been performed and there are at least 4 reviews on its use in IC⁴⁹⁻⁵². The trials were of varying quality. The results were contradictory and in general modest. In the latest systematic review⁵¹, only 2 of 18 trials were of acceptable quality, providing very modest and statistically insignificant results for PFWD (n=150, 15m, -5-35 and n=40, -30m, -138-78 and for MWD (n=150, 21m, -10-52, and n=40, 69m, -44-182). In 2002, 4 new trials appeared on the use of pentoxifylline for IC, all performed by the same group⁵³⁻⁵⁶. They report significant positive results for PFWD (38% increase vs placebo) and MWD (38-124% increase vs placebo). These trials have not yet been peer reviewed. A protocol of pentoxifylline in IC has been published for several years, but the systematic review is still awaited⁵⁷.

Side effects include vasomotor flushing, gastro-intestinal disturbances, bleeding, and hypersensitivity reactions.

For now, there is insufficient evidence for benefit of pentoxifylline in IC.

III. Drugs limited by lack of evidence:

There is no indication for their recommendation in the treatment of IC because there are either no RCTs or none showing efficacy. This conclusion can be reversed by results of high quality trials on symptoms, disease modification, or hard endpoints.

Conclusions

1. There still is a role for symptomatic pharmacological treatment of IC in its own right.
2. The drugs that currently qualify are: naftidrofuryl and cilostazol. Both have been analysed in a Cochrane review. In the absence of comparative head to head trials or a mixed method analysis, it is up to the reader to judge their benefits and risks.
3. In general, it is not because a product is old that it should not be (re)subjected to a thorough review. It should be considered not to renew licenses of drugs for which we fail to deliver convincing evidence of a satisfactory benefit/risk ratio. This could be discussed in following conditions: a) initial claims of efficacy and efficiency are not corroborated as experience accumulates, and /or b) halted research activity fails to deliver confirmation of effect and/or c) no other convincing indications emerge and/or d. there is a toxicity or safety issue.
4. Future trials on symptomatic treatment of IC should include walking distances besides quality of life.

5. As economic resources are limited, besides efficacy and safety, cost-effectiveness should be included in the analysis, based on recent data of efficacy, safety and direct and indirect health care costs.

Table. Classification of vasoactive products in the symptomatic treatment of intermittent claudication evaluated through randomised, placebo-controlled, double-blind trials.

I. Drugs with an evidence base supporting claims of efficacy on symptoms of IC		
cilostazol	naftidrofuryl	statins*
II. Drugs with limited and/or doubtful evidence of efficacy on symptoms of IC		
angiogenesis growth factors	ACE-inhibitors*	L-arginine
aspirin*	buflomedil	Propriionyl-L-carnitine
clopidogrel*	cloricromene	dipyridamole
gingko biloba	mesoglycan	pentoxifylline
picotamide	policosanol	prostaglandins
ticlopidine*	verapamil	vitamin E
III. Drugs with no evidence of efficacy on IC		
pure arteriolar vasodilators	cinnarazine	cyclandelate
isoxsuprine	ketanserine	xantinol nicotinate

*: These drugs have evidence for use in the standard treatment of peripheral arterial disease

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